REMARKS

Status of Claims

Claims 1-12, 17-42, 45, and 48-50 are canceled without prejudice to their prosecution in any continuation or divisional application. Support for amended claims 13, 43, 44, 46, and 47, as well as new claims 51-62, is found in the specification at page 1, lines 8-14 and 27-28; page 2, lines 1-9; page 4, lines 15-20; page 7, lines 1-8; page 8, lines 18-22; page 9, lines 14-27; page 10, lines 3-11 and 20-30; page 11, 1ines 1-20; pages 12-16; page 20, lines 9-15; page 21, lines 14-21; and Examples 6 and 7. Upon entry of the amendment, claims 13-16, 43, 44, 46, 47, and 51-62 are present and active in the application. No new matter has been added.

Interview Summary

Applicants thank Examiner Huynh for the courteous and helpful discussion with Applicants' representative on September 19, 2006. During the discussion, possible claim language amendments were discussed with regard to distinguishing the invention from the art of record.

Request for Reconsideration

Above-average levels of apoptotic bodies in the bloodstream have been correlated with the presence of tumors and cancers in a subject. While this statement appears to contradict the general observation that apoptotic levels are decreased in tumor and cancer cells, the statement is not absolute. Resistance to apoptosis is usually a late event in malignant progression--that is, resistance to apoptosis increases as the cancer grows and becomes metastatic. Therefore, early stage tumors can be characterized by slow overall growth, reflecting a high proliferation rate balanced by a high level of apoptosis. Even in late stage tumors with relatively low rates of apoptosis, the absolute number of apoptotic bodies can be high due to the large tumor mass.

Nucleolin and PARP-1 have been discovered to be unexpectedly convenient and reliable markers for the detection of apoptotic bodies, especially those shed into circulation. Detecting these antigens in circulation, such as in plasma or serum,

correlates with levels of apoptosis that overwhelm the usual apoptotic body-clearing systems, such as macrophages and/or neighboring cells to the site of apoptosis.

Normal, healthy subjects have undetectable levels of apoptotic bodies in the circulation, because the usual apoptotic body-clearing mechanisms would remove them before they accumulate to detectable levels. Consequently, nucleolin and PARP-1 are undetectable in the circulation of healthy subjects. The detection of nucleolin or PARP-1 in the circulation means that high levels of these proteins are present in the circulation, which correlates with excessive apoptosis.

The invention as now claimed is directed to two methods for detecting excessive apoptosis in a blood sample from a subject. One method includes reacting an antibody that binds specifically to nucleolin, to detect apoptotic bodies in the blood sample, wherein detecting high levels of nucleolin correlates with excessive apoptosis. The second method includes reacting an antibody that binds specifically to poly(ADP-ribose) polymerase (PARP-1), to detect apoptotic bodies in the blood sample, wherein detecting high levels of PARP-1 correlates with excessive apoptosis.

The rejections of the claims under 35 U.S.C. § 102(b) over Martelli et al., and under 35 U.S.C. § 103(a) over Martelli et al. in view of U.S. Patent No. 6,350,452 to Riss, or in view of U.S. Patent No. 6,096,532 to Armstrong et al., or in view of Rosenthal et al. (Nucleic Acids Res. 25(7):1437-41 (1997) have been obviated in part by appropriate amendment or by cancellation of the relevant claims. Martelli et al. and Riss do not describe or suggest reacting a blood sample with an antibody that binds specifically to either nucleolin or poly(ADP-ribose) polymerase (PARP-1), to detect apoptotic bodies in the blood sample, wherein detecting nucleolin or PARP-1 correlates with excessive apoptosis.

Martelli et al. concerns the intracellular distribution of the nucleolar protein components during the apoptosis process in camptothecin-treated HL60 cells. Martelli et al. does not correlate either nucleolin or PARP-1 in a blood sample to detect excessive apoptosis.

Riss describes using an antibody against the cleaved 89kD PARP-1 product as a marker for apoptosis in cultured HL60 cells. Riss does not correlate either nucleolin or PARP-1 in a blood sample to detect excessive apoptosis.

The present invention includes reacting a blood sample with an antibody that binds specifically to either nucleolin or poly(ADP-ribose) polymerase (PARP-1), to detect apoptotic bodies in the blood sample, wherein detecting nucleolin or PARP-1 correlates with excessive apoptosis. Neither Martelli et al. nor Riss teaches this feature of the claimed invention. Both Armstrong et al. and Rosenthal et al. have been cited only for elements of dependent claims. Applicants submit that the claimed invention is neither anticipated by, nor obvious over, the applied references.

The rejections of claims 1-6, 10-12, and 40-50 under 35 U.S.C. § 112, first paragraph, have been obviated by appropriate amendment or by cancellation of the relevant claims.

The rejections of claims 1-6, 10-16, and 40-50 under 35 U.S.C. § 112, second paragraph, have been obviated by appropriate amendment or by cancellation of the relevant claims.

Applicants submit that the application is now in condition for allowance. Applicants encourage Dr. Huynh to contact the undersigned by telephone to discuss subject matter that may be allowable following entry of this amendment or by way of entry of an Examiner's amendment. Early notice of such action is earnestly solicited.

Respectfully submitted,

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